From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052028	03.09.2004	03.09.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/505, A61K31/52, A61K31/513, A61P31/18

Applicant
TIBOTEC PHARMACEUTICALS LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Rodriguez-Palmero, M Telephone No. +49 89 2399-7871

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication:

   D1: WO 03 016306 A (KOYMANS LUCIEN MARIA HENRICUS ;LEWI PAULUS JOANNES (BE); VAN AKEN) 27 February 2003.

   D2: PAVIA AT: "Abacavir/Lamivudine in Combination with Efavirenz, Amprenavir/Ritonavir or Stavudine" INTERNET ARTICLE, [Online] 9 July 2002 (2002-07-09), Retrieved from the Internet: <URL:http://www.thebody.com/confs/aids2002 /pavia5.html> [retrieved on 2004-03-23]

   D3: GILEAD SCIENCES INC.: "Gilead initiates study 934, a 48-week clinical trial evaluating VireadTM and EmtrivaTM versus CombivirTM" INTERNET ARTICLE, [Online] 11 August 2003 (2003-08-11), XP002314669 Retrieved from the Internet: URL:http://www.gilead.com/wt/sec/pr_106063 1111> [retrieved on 2005-01-24]

1.1 Unless indicated, reference is made to the passages indicated in the international search report.

2. **Novelty (Art. 33(2) PCT)**

   The present application relates to a combination comprising 4-[[4-[[4-(2-cyano-ethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile (TMC278) and a nucleoside reverse transcriptase inhibitor (NRTI) and/or a nucleotide reverse transcriptase inhibitor (NtRTI) for the prevention or treatment of HIV infection.

   None of the prior art documents cited in the search report discloses such a combination. Therefore, the subject-matter of present claims 1-24 is considered novel in the light of the documents of the search report.

3. **Inventive Step (Art. 33(3) PCT)**

3.1 D1, which is considered to represent the closest prior art document, discloses the E and Z-isomeric forms of TMC278 (see compounds 1 and 10, respectively). The compounds disclosed therein are mentioned to be effective for treatment or prevention of HIV infections (see page 51, lines 12-28), also against (multi) drug resistant HIV-1 strains (see page 43, lines 20-29). D1 also mentions the combination of the compounds disclosed therein with other antiretroviral compounds, including NRTIs such as lamivudine (3TC) and abacavir and NtRTIs such as tenofovir (see page 51, line 25 - page 52, line 13).

3.2 A combination of active principles which are already known for a certain therapeutic application can only be considered to involve an inventive step if a synergistic effect resulting from that combination can be shown. However, the present application lacks any technical data showing the effect of the combination claimed. Consequently, the subject-matter of present claims 1-24 is not considered to involve an inventive step in the light of D1.

3.3 Moreover, the following should be taken into consideration:

D2 discloses the use of a backbone comprising abacavir and 3TC together with a non-nucleoside reverse transcriptase inhibitor (NNRTI; efavirenz), a phosphatase inhibitor (PI; amprevavir/ritonavir) or a NRTI (stavudine). It discloses that the NNRTI-containing regimen for initial therapy was at least as effective as other approaches with better tolerability.

D3 discloses the announcement that the company Gilead Sciences has initiated the Study 934 to assess the efficacy of a once-daily regimen contianing Viread® (tenofovir disoproxil fumarate) and Emtriva™ (emtricitabine) in combination with efavirenz.

Therefore, D2 and D3 show that the backbones comprising abacavir/3TC and tenofovir/emtricitabine and their combination with a NNRTI (in that case efavirenz) are already known in the art. Therefore, the subject-matter of present claims 1-24 is also not considered to involve an inventive step in the light of D1 in combination with

D2 or D3.

4. **Industrial applicability (Art. 33(4) PCT)**

Present claims 1-24 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.